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MULTIPLE SCLEROSIS

Report on 200 cases from Curitiba, Southern Brazil and comparison with other Brazilian series

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ABSTRACT – We reviewed the clinical and laboratorial findings of 200 patients in Curitiba, Southern Brazil (25°25'40" S; 49°16'23" W-GR), with multiple sclerosis (MS)according to Poser's criteria. The patients were classified as: clinically definite (A1 and A2) – 142 patients (71%); laboratory-supported definite – 42 patients (21%); and clinically probable – 16 patients (8%). Relapsing-remitting (RR) form was the most common clinical presentation, with 182 (91%), followed by primary progressive (PP)(16 cases, 8%), and only 2 cases with secondarily progressive form (SP). Nine women and 7 men totalized the 16 PP cases. The mean age of onset was 32.0±9.9 (median 32 years). The gender ratio was female 1.8:1 male. All patients, except 3 African-Brazilian, were white. Seven (3.5%) patients developed a clinical history of Devic´s syndrome. The initial clinical picture included brainstem/cerebellar syndrome in 126 (63%) cases, sensorial findings in 106 (53%)patients, motor (pyramidal) syndrome in 102 (49.5%), and optic neuritis in 79 (39.5%) cases. 122 (61%) patients had a final EDSS score < 3.5; 45 (22.5%) a score between 3.5 and 5.5, and 33 (16.5%) a score ≥ 6.0. There was no significant correlation between the number of relapses or duration of disease with EDSS scores (Spearman's test). Only 14 (7%) of the total number presented the benign form (EDSS< 3.5 after 10 years of disease). We observed a later age of onset and initial clinical findings with higher frequency of brainstem/ cerebellar syndrome and optic neuritis, when compared to other Brazilian and Western series

KEY WORDS: multiple sclerosis, clinical forms, Brazilian series, EDSS.

Esclerose múltipla: descrição de 200 casos de Curitiba, Paraná e comparação com outras séries brasileiras

RESUMO – Os autores analisaram retrospectivamente 200 pacientes portadores de esclerose múltipla de acordo com os critérios de Poser (1983). Cento e quarenta e dois (71%) dos casos possuíam a forma clinicamente definida, 42 (21%) a forma definida laboratorialmente e 16 (8%) a forma clinicamente provável. A forma recorrente-remitente (RR) foi a mais comumente observada (182 casos, 91%), seguida pela forma progressiva primária (PP)(16 casos, 8%), e somente 2 pacientes com a forma secundariamente progressiva. A idade média de início da doença foi 32,0±9,9 anos (mediana 32 anos).A relação entre os gêneros foi mulheres 1,8:1 homens. Todos os pacientes eram da raça branca, com exceção de 3 pacientes afro-brasileiros. Síndrome de Devic ou neuromielite óptica foi observada em 7 (3,5%) pacientes. Síndrome de tronco cerebral/cerebelar foi a forma mais comum de apresentação inicial da doença, com 126 casos (63%), seguido por achados sensoriais (106 casos, 53%), síndrome motora/piramidal (102 casos, 49,5%), e neurite óptica (79 casos, 39,5%). Nesta série, 122 pacientes (61%) possuíam um EDSS final < 3,5; 45 (22,5%) escore entre 3,5 e 5,5 e 33 (16,5%) um escore ≥ 6.0. Não se observou uma correlação entre o número de surtos ou os anos de doença com o escore EDSS (teste de Spearman). Somente 14 pacientes (7%) possuíam a forma benigna de esclerose múltipla (escore EDSS < 3,5 após 10 anos de doença).Comparada com outras séries brasileiras, a nossa série diferenciou-se em alguns aspectos como idade mais tardia de início da doença e forma clínica de apresentação inicial com maior frequência de envolvimento de nervo óptico e tronco cerebral/cerebelo. Estas observações devem-se provavelmente a fatores locais de seleção dos pacientes encaminhados ao Hospital Universitário de Curitiba, assim como possivelmente à diferente constituição étnica-racial da população local, quando comparada com populações de São Paulo, Rio de Janeiro e Minas Gerais.

PALAVRAS-CHAVE: esclerose múltipla, formas clínicas, séries brasileiras, EDSS.

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Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system (CNS) that shows a wide range of clinical features and natural history. The variation in prevalence and clinical pattern according to geographical location, probably related to ethnic and environmental factors, have been observed in several studies[1,2].

The present report describes 200 patients with diagnosis of MS seen at the University Hospital of the Universidade Federal do Paraná, Curitiba, Brazil. Our findings are discussed in light of other series of MS patients reported in Brazil.

METHOD

The 200 patients were selected from a review of all cases with diagnosis of MS performed in the Hospital de Clínicas, Universidade Federal do Paraná, Curitiba, Brazil. Curitiba is a 1,550,317 people city located in Southern Brazil (approximately Paralel 25 South).

After reviewing all medical records of patients seen in the period between 1975 and 1999, all patients satisfying the Poser criteria[3] were included. For primary progressive form (PP), we adopted the criteria recently proposed by Thompson et al.[4]. All patients with a clinical condition that could potentially cause the neurological clinical and/or laboratory findings were excluded (e.g. lupus erythematosus, Behçet disease, Sjögren disease, vasculitis, HIV infection, syphilis, CADASIL). Disability was measured using EDSS scores as described by Kurtzke[5].

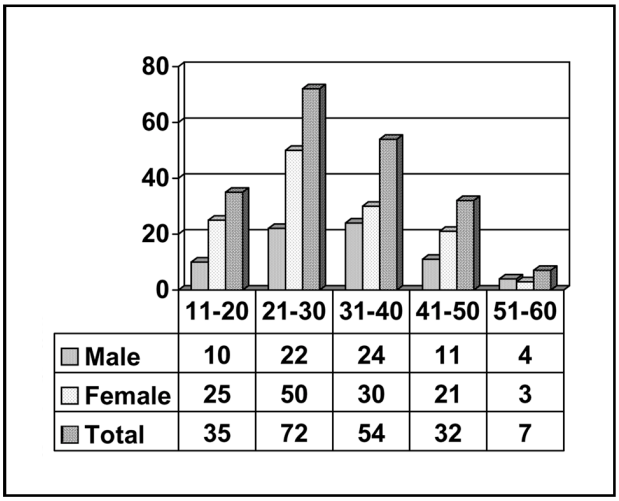
Statistical analysis included t Student test and non-parametric statistics (Spearman's test).

RESULTS

According to the classification of Poser[3], the patients were distributed as shown as follows:clinically definite (A1 and A2) – 142 patients (71%); laboratory-supported definite – 42 patients (21%); and clinically probable – 16 patients (8%).

Relapsing-remitting (RR) form was the most common clinical presentation, with 182 (91%), followed by primary progressive (PP)(16 cases, 8%), and only 2 cases with secondarily progressive form (SP). Nine women and 7 men totalized the 16 PP cases. The mean age of onset in this group was 32.0±9.9 (median 32.0 years).

The mean age of onset of the entire group of 200 patients was 32.0±9.9 years (median 32); in women the mean age onset was 30.0±9.9 years (median 28,0) and men had a mean age of onset of 32.5±10.6 years (median 32). Figure 1 shows the distribution of number of cases per decade and according to gender. There was a larger proportion of women, who represented 64.5% (129 cases), giving a gender ratio of female 1,8:1 male. Only 3 patients



	11-20	21-30	31-40	41-50	51-60
Male	10	22	24	11	4
Female	25	50	30	21	3
Total	35	72	54	32	7

Fig 1. Distribution of 200 MS patients by age and gender.

were African-Brazilian; there were no cases of Asiatic ancestry. All other patients were white. Only 3 patients had a positive family history of MS (each one with one first degree affected relative).

Cerebrospinal fluid (CSF) examination was performed in 74 patients. It was normal in 43 cases; mononuclear hypercytosis occurred in 4 cases, increased CSF protein is 3 cases, and increased gammaglobulin fraction (cellulose electrophoresis) or increased IgG index in 24 cases. HTLV-1 antibodies were tested in 10 patients and were negative in all samples. Blood and CSF VDRL were negative in all cases. Blood VDRL was tested in all 200 cases.

Visual evoked potential were performed in 36 patients, and it was abnormal and in keeping with a demyelinating disorder in 24 cases. Brainstem and somatosensory evoked potentials were obtained in 10 and 6 cases, respectively, and it was abnormal in only 2 cases for each test.

Twenty-one computed tomography (CT) scans were done and the findings were: normal in 9 patients, findings in keeping with a white matter disease in 8, enlarged cerebral sulci in 2, isolated calcification 1, and mild ventricular dilatation in 1.

Fourty-seven patients underwent head magnetic resonance imaging (MRI); in 43 (91.5%) the findings were compatible with MS[6]. Fifteen cervical spine MRI were done and showed demyelinating lesions in 12 (80%). Six patients had both head and cervical MRI examination disclosing demyelinating lesions. In 4 cases, the head MRI was normal, but the cervical spine MRI showed multiple lesions[7]. In 2 cases, the head MRI was abnormal and the cervical spine examination was normal. Table 1 shows the initial clinical picture of this series. Brown-Séquard syndrome at level T8 was the clinical initial picture in

Table 1. Initial syndromic presentation in 200 cases of MS.

Symptoms/signs	Number of cases (%)
Brainstem/cerebellar	126 (63)
Sensory	106 (53)
Motor	99 (49.5)
Optic neuritis	79 (39.5)

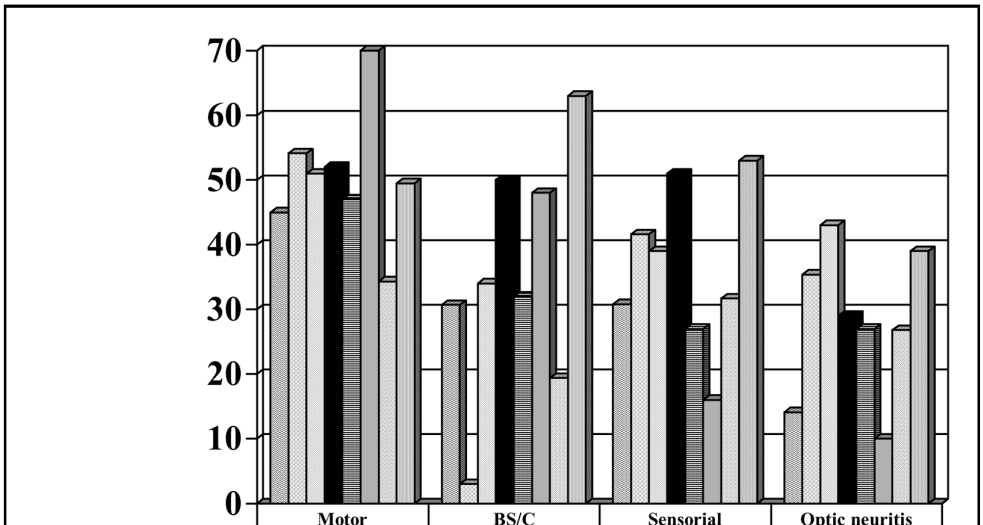
only one patient. Seven (3.5%) patients developed a clinical history of Devic´s syndrome. Two patients developed their first relapse during pregnancy and puerperal period (each one). In six (3%) patients, bilateral optic neuritis occurred at onset.

Table 2 depicts the clinical findings at the last evaluation. More than one finding might have been present at that time.

We observed that 122 (61%) patients had a final EDSS score < 3.5; 45 (22.5%) a score between 3.5 and 5.5, and 33 (16.5%) a score ≥ 6.0. There was no correlation between the number of relapses or duration of disease with EDSS scores (Spearman's test) (Figs 3 and 4). This observation did not change after the exclusion of benign cases. Only 14 (7%) of the total number presented the benign form according to the definition proposed by Weinshenker[8] (EDSS< 3.5 after 10 years of disease).

Table 2. Clinical findings: last evaluation.

Final clinical picture	Number of cases
Optic neuritis / optic atrophy	87/31
Isolated cranial palsy (III, IV, VI)	63
V cranial nerve involvement	48
Internuclear ophthalmoplegia	15
Dizziness	24
Limb ataxia	68
Truncal ataxia	41
Paraplegia	82
Permanent motor deficits (mono, hemi, tetra)	73
Sensory deficits	156
Dysphagia	9
Dyspnea	1
Urinary disturbance	59
Severe chronic constipation	3
Fecal incontinence	7
Dementia	1



	Motor	BS/C	Sensorial	Optic neuritis
Callegaro, 1989	45	30,7	30,8	14,1
Leite, 1990	54,1	3	41,6	35,4
Lana-Peixoto, 1992	51	34	39	43
Papaiz-Alvarenga, 1995	52	50	51	29
Tilbery, 1995	47	32	27	27
Oliveira, 1999	70	48	16	10
Moreira, 2000	34,3	19,4	31,7	26,8
Present series	49,5	63	53	39

Fig 2. Clinical syndromes at onset of MS in Brazilian series.

Table 3. Clinical features of other Brazilian series and present series.

	Nr.	Gender ratio F:M	Mean age of onset	Race	Clinical form	Poser criteria
Callegaro[9]	120	1.6:1	27.9±8.9*	79.2% W 10% M 10% B 0.8% Y	85% RR 10.2% PP 4.2% SP	Definite MS
Leite[10]	51	2.1:1	34.5±13.9	62.7% W 37.4% non-white	47% RR 19.7% PP 33.3% "mixed"	45 Definite MS 6 Probable
Lana-Peixoto[11]	67	2.3:1	28.9±10.4**	76% W 19.4% M 4.5% B	-	Definite MS
Papaiz-Alvarenga[12,13]	88	3:1	27.9±11.3*	68.2% W 31.8% B	88.6% RR 4.5% PP 6.8 SP	A - 74% B - 5.3% C - 17.8%
Tilbery[14]	214	2.9-1	28 (RR) 36 (PP)	96% W 4.2%B 0.5% Y	82 % RR 18% PP	Definite MS
Oliveira[15]	50	2:1	32.5±9.6	64% W 34% M+B 2% Y	60% RR 30% PP 10% SP	76% definite 24% probable
Moreira[16]	302	3.1:1	37.7	94% W 5% B 1% Y	72% RR 14% PP 14% SP	Definite MS
Present series	200	1.8:1	32.0±9.9	98.5% W 1.5% B	91% RR 8% PP 1% SP	A - 61% B – 21% C – 8%

W, White; B, Black; M, Mulato; Y, Asian; RR, Relapsing-remitting form; PP, primary progressive form; SP, secondarily-progressive form.
t Student test: *p<0,0005; **p<0.05, when compred with the present series.

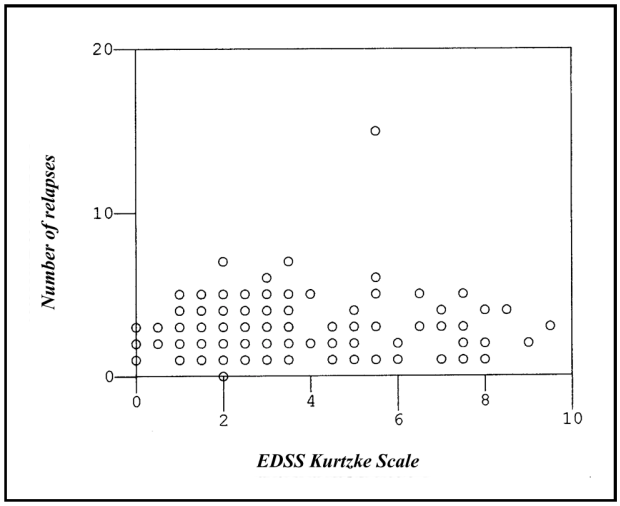


Fig 3. Number of relapses and EDSS score. Spearman´s test showed no statistically significant correlation.

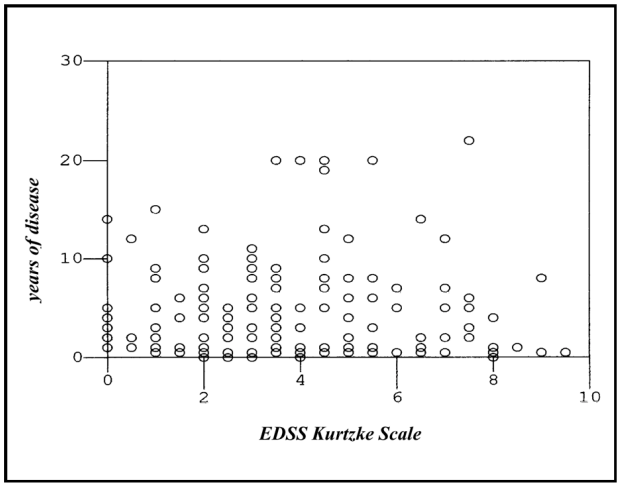


Fig 4. Duration of disease (years) and EDSS score. Spearman´s test showed no statistically significant correlation.

DISCUSSION

Table 3 and Figure 2 depicts some features from other Brazilian series and ours.

Comparison of clinical data from several retrospective series of MS patients may be a daunting task[9,10] for several reasons: first, ascertainment bias probably play a major role in some observed differences; the reasons for that is, to some extent, different criteria of inclusion (though all series mentioned the Poser criteria), different local characteristics of the Services, e.g. the study of Belo Horizonte[11] is from a strong referal Service of Neuro-ophthalmology; and different racial composition of these centers. For instance, the series from Rio de Janeiro[12,13] has a much larger proportion of black patients (Afro-Brazilian), whilst our own series showed a clear preponderance of white patients. In all series there is a higher proportion of female to male patients. Due to the marked racial miscigenation, it is even difficult to categorize some patients. In all series, a distinction of white Latinos and white Caucasian is not made. Nevertheless, there is a clear predominance of white race, as well as a similar female to male ratio. The relapsing-remitting form (RR) is the most common form, followed by primary progressive form. There is a marked difference of frequency in the PP forms – again, it is conceivable that this different is more related to bias of selection than other environmental or racial factors. It is also conceivable that the use of different clinical criteria may explain to some extent this difference. In all series, including ours, there is a tendency for a later age of onset in the PP forms, and the female:male proportion tends to be equal.

Our group of patients presented a higher mean age of onset when compared to three other series[11,13,14].This might be related to a longer interval of time between onset of disease and clinical diagnosis. The increasing availability of MR imaging tends to decrease this time gap.

In terms of clinical presentation, pyramidal findings and optic neuritis occur in approximately equal proportions in all series, except for a much higher frequency of pyramidal syndrome and lower frequency of optic neurits at disease's onset in Oliveira's series[15]. Perhaps their larger number of patients with PP form may partially account for this difference (30% versus 8 to 19% in other series).

Brainstem/cerebellar syndromes and sensorial findings occured in much variable proportions in the other series. Our high frequency of brainstem/cerebellar symptomatology (63%) at disease's onset in our patients might be owing to different registering methods of clinical findings rather than implying a true clinical heterogeneity between the clinical series.

Neuromyelitis optica form has been reported to occur more frequently in African American and Asian type MS patients[16,17]. Papaiz-Alvarenga[12,13], who had the series with the largest proportion of African Brazilian (31.8%) patients reported 5.6% with this clinical form, Leite et al.[10] had 15.6%, whereas Lana-Peixoto[11], with 24 % of African Brazilian patients, reported a prevalence of 12% with Devic´s syndrome and suggested that his patients thus presented a clinical form more alike the Asian MS patients. We observed only 3.5% of our patients with this clinical form, and this observation may be explained by the very low proportion of either African-Brazilian and Asiatic elements. On the other hand, we had a high number of patients with optic neuritis as their initial symptom (39.5%). This frequency is somewhat higher than in other Western series and similar to some Brazilian series[10,11] and Asian series. There is no explanation for this observation based on the current available genetic racial data in our series. It seems pointless, at this time, to try defining our series as having a Western or Asian pattern. Apart the methodological difficulties already mentioned, other racial/genetic and environmental factors may play a role in leading to these observations. In order to delineate the clinical profile of MS in Brazil, a prospective study about the natural history of MS is being conducted by the Brazilian Committee for Treatment and Research in Multiple Sclerosis (BCTRIMS).

The variation in the clinical presentation of MS and the course of the disease is well recognised. In most patients the condition has a RR course at first, but after a variable period progressive disability occurs, often with superimposed relapses (secondary progressive disease). Our extremely low number (1%) of patients with SP form conceivably reflects a short time of follow-up and bias of selection.

In about 30% of patients the disease follows a fairly benign course and appreciable disability has not developed 10 to 15 years after its onset. However, using different criteria[18], Moreira et al.[16] found 19.8% of their patients with the benign form, compared to only 7% in our series[8]. The diagnosis of benign form is a retrospective one, and again the

time of individual follow-up in different Services may account for such differences.

The poor correlation of EDSS scale and time of disease and number of relapses observed in our series reflects the difficult issue of prediction of upcoming disability and the therapeutic decisions derived from it[19]. EDSS Kurtzke scale remains by far the most widely used scoring system in MS despite some perceived problems[20,21]. The development of combined analysis of clinical rating systems, envolving some aspects of neurological function in more detail than the EDSS, with more reliable and consistent MRI techniques may improve the evaluation of progression of the disease[20-22].

Kira et al.[23] observed that DR2-associated DRB1*1501 allele and DRB5*0101 allele were associated with Western-type MS, but not with Asian-type MS, in their Japanese MS patients. Alves-Leon[24] studied 44 African-Brazilian MS patients living in Rio de Janeiro, and observed a significantly higher proportion of HLA-DQB1*0602 allele (MS 45% versus 17% controls). Papais-Alvarenga et al.[25] recently showed that DR2 haplotype (DRB1*1501-DQB1*0602) also confered genetic suceptibility to white MS Brazilian patients in Rio de Janeiro. Finally, the mode of transmission of genetic susceptibility to MS is complex and might include other genes than the HLA system (a polygenic disease)[26-28].

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